RESEARCH PAPER

In Vivo Pharmacokinetic Evaluation and *In Vitro-In Vivo* Correlation of a Sulphated Locust Bean Gum and Cationic Guar Gum Polyelectrolyte Complex Based Controlled Release Tablet of Losartan Potassium in Rabbits

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Received: 28th May, 2026; Revised: 24nd June 2026; Accepted: 24nd June, 2026; Available Online: 31th August, 2026

ABSTRACT

Background: Losartan potassium (LP), a widely prescribed angiotensin II receptor blocker, is characterized by low oral bioavailability (~33%) and a short elimination half life (1.5-2.5 h), which together necessitate frequent daily dosing. A controlled-release (CR) tablet formulation of LP (LPC), based on a polyelectrolyte complex (PEC) of sulphated locust bean gum (SLBG) and cationic guar gum (CGG), was previously optimised by Box-Behnken design and shown to sustain in vitro drug release for 12 h. The present study evaluated the in vivo performance of a rabbit equivalent dose PEC tablet (RLPC) and established an in vitro–in vivo correlation (IVIVC). ***Methods***: The rabbit equivalent dose was estimated by the body surface area conversion method, and RLPC tablets were prepared by proportionate downscaling of the optimised LPC formula. A single dose, parallel group pharmacokinetic study was conducted in healthy male rabbits (n = 6/group) that received either a pure LP dispersion (reference) or RLPC tablets (test) by oral gavage. Serial blood samples were withdrawn from the marginal ear vein over 24 h, and plasma LP was quantified by a validated HPLC-PDA method. Non-compartmental pharmacokinetic parameters were derived, group differences were tested by an unpaired Student's t-test, and a Level A IVIVC was constructed between in vitro fraction dissolved and in vivo fraction absorbed. ***Results***: RLPC produced a lower peak plasma concentration (Cmax 304.33 vs 356.42 ng/mL) with a markedly delayed time to peak (Tmax 6 vs 1 h) relative to the pure drug. Systemic exposure was significantly greater for RLPC, with AUC0–∞ rising from 1113.81 to 4201.65 ng·h/mL (~3.8-fold) and mean residence time increasing from 3.41 to 9.52 h ($p < 0.05$). Elimination rate constant and half life were not significantly different between treatments ($p > 0.05$), indicating that the intrinsic elimination of LP was unaffected by the PEC matrix. A strong Level A IVIVC was obtained ($R^2 = 0.9919$). ***Conclusion***: The PEC formed between SLBG and CGG effectively sustained the in vivo release of losartan potassium, producing a controlled release pharmacokinetic profile with a good in vitro–in vivo relationship, supporting its potential as a release retarding matrix for oral controlled release drug delivery.

Keywords: Losartan potassium; Polyelectrolyte complex; Controlled release tablet; Rabbit pharmacokinetics; In vitro–in vivo correlation; Natural polysaccharide gums.

How to cite this article: D. Purnima Yadav1* Dr. N. Lakshmi Prasanthi2 Prof. G. Girija Sankar3 Dr. K. V. Ramana Murthy4. In Vivo Pharmacokinetic Evaluation and In Vitro-In Vivo Correlation of a Sulphated Locust Bean Gum and Cationic Guar Gum Polyelectrolyte Complex Based Controlled Release Tablet of Losartan Potassium in Rabbits. Int J Drug Deliv Technol. 2026;16(80s):597-598. DOI: 10.25258/ijddt.16.80s.73

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

Losartan potassium (LP) is the first orally active, non-peptide angiotensin II type-1 receptor antagonist introduced for the management of essential hypertension and related cardiovascular and renal conditions. Despite its well-established clinical efficacy, LP undergoes extensive hepatic first-pass metabolism mediated by cytochrome P450 isoenzymes 2C9 and 3A4, which limits its systemic bioavailability to approximately 33% and confers a short elimination half life of 1.5-2.5 h[1]. Consequently, conventional immediate release LP tablets require once- or twice-daily administration, and the resulting fluctuations between peak and trough plasma concentrations can compromise sustained blood pressure control and patient adherence. A controlled release (CR) delivery system capable of prolonging and moderating drug release across the gastrointestinal tract is therefore pharmacologically rational for this drug, since it can flatten the plasma concentration-time profile, reduce dosing frequency, and improve compliance in a condition that demands long term therapy.

Natural polysaccharide gums are increasingly explored as release retarding matrices in oral CR dosage forms because of their biocompatibility, biodegradability, low cost, and tunable hydration and gelling behaviour. Polyelectrolyte complexes (PECs), formed through electrostatic interaction between oppositely charged polysaccharides, generate a cohesive, pH-responsive gel network that can resist rapid erosion and premature drug release more effectively than a single polymer matrix. In an earlier phase of this investigation, an LP controlled release tablet (LPC) was optimized using a PEC formed between an anionic derivative, sulphated locust bean gum (SLBG), and a cationic derivative, cationic guar gum (CGG), together with microcrystalline cellulose (MCC) as a diluent, through Box-Behnken design and response surface methodology. The optimized formulation (57.76 mg SLBG, 46.12 mg CGG and 38.91 mg MCC per tablet) released 23.01% of the drug at 2 h and 90% at 10 h, sustaining release over 10 h while withstanding the acidic pH of the simulated gastric

environment.

Although this *in vitro* release performance supported the intended CR design, the gastrointestinal environment is subject to considerable physiological variability in pH, motility, transit time, and enzymatic activity that can alter drug release and absorption in ways not captured by *in vitro* testing alone. An *in vivo* pharmacokinetic evaluation was therefore undertaken to confirm that the controlled release characteristics of the optimized PEC tablet translate into a corresponding modification of the plasma concentration-time profile.

The rabbit was selected as the preclinical model for this evaluation. Its comparatively large body size and circulating blood volume permit serial blood collection from the same animal over an extended sampling schedule, allowing a complete individual plasma concentration-time profile to be generated without compromising animal welfare. In contrast, the limited blood volume of rats, and particularly mice, restricts both the frequency and volume of repeated sampling and typically necessitates a composite, one animal per time point design[2,3]. Rabbits are additionally established as a practical and cost effective species for oral bioavailability and controlled release evaluation, and losartan potassium formulations including floating and matrix type systems have previously been characterized pharmacokinetically in this species[2], supporting the suitability of the rabbit for the present investigation.

The objective of the present study was, therefore, to (i) determine a rabbit equivalent dose of the optimized LP polyelectrolyte complex tablet and confirm that *in vitro* release characteristics were preserved on downscaling, (ii) evaluate its *in vivo* pharmacokinetic performance against a pure drug reference in a parallel-group rabbit model, and (iii) establish a Level A *in vitro in vivo* correlation to assess whether the in vitro dissolution test can serve as a surrogate predictor of the formulation's in vivo absorption behaviour.

MATERIALS AND METHODS

2.1. Materials

Losartan potassium was procured from Dharmtech Pharma and Consultants, Maharashtra. Cationic guar gum was purchased from Chimique India limited, Haryana, India, and locust bean gum from PY Chemical industries, Gujarat India. All other excipients and reagents were of analytical grade and were purchased from Sigma-Aldrich, Bangalore, India. Acetonitrile and other reagents used for sample preparation and chromatographic analysis were of analytical or HPLC grade and purchased from Sigma-Aldrich, Bangalore, India.

2.2. Rabbit dose calculation

The rabbit equivalent dose was estimated by the body surface area normalization method recommended in the United States Food and Drug Administration (FDA) guidance on estimating the maximum safe starting dose in initial clinical trials, whereby the human effective dose (mg/kg) is divided by a species specific conversion factor of 0.32 for rabbits[4]. The LPC tablets contained 50 mg of losartan potassium, and an average human body weight of 60 kg was assumed for dose normalization, consistent with the same assumption used for the preclinical dose calculation. The corresponding calculation was as follows:

Human dose = 50 mg / 60 kg = 0.833 mg/kg

Rabbit dose = 0.833 / 0.32 ≈ 2.603 mg/kg body weight

Dose for a rabbit weighing ~2.5 kg = 2.603 × 2.5 = 6.51 ≈ 6.5 mg

2.3. Animals

Healthy male rabbits with an average body weight of 2.5 kg were used for the study. Animals were housed under standard laboratory conditions with free access to feed and water ad libitum and were acclimatized for one week before the start of the study.

2.4. Preparation and evaluation of the rabbit-dose polyelectrolyte complex tablet (RLPC)

2.4.1. Preparation of the SLBG-CGG polyelectrolyte complex

The polyelectrolyte complex (PEC) used for tablet preparation was generated by controlled electrostatic interaction between the anionic and cationic polysaccharide derivatives. SLBG and CGG were each dissolved separately in 50 mL distilled water each to prepare polymer dispersions. SLBG dispersion was added dropwise into the CGG dispersion under continuous stirring, as per the ratio of polymer weights specified in Table 1. The combined dispersion was stirred continuously at room temperature for 1 h to allow complexation between the oppositely charged polymers, and the resulting suspension was then incubated for 24 h at 37°C in a shaking incubator to permit maturation of the complex. The precipitated PEC was recovered by centrifugation at 6000 rpm for 10 min and washed with distilled water to remove residual, uncomplexed polymer. The washed wet mass was dried in a hot-air oven at 50-60°C to constant weight, after which the dried complex was milled and passed through a #40 mesh sieve (ASTM E11; 250 µm aperture) to obtain a fine powder of uniform particle size suitable for compression.

2.4.2. Preparation and evaluation of RLPC tablets

The optimised LPC formula was proportionately downscaled to the calculated rabbit-equivalent dose to obtain the RLPC tablet composition (Table 1), intended for oral administration to rabbits of approximately 2.5 kg body weight. RLPC tablets were prepared using the SLBG-CGG polyelectrolyte complex described above, blended with the downscaled proportions of microcrystalline cellulose, magnesium stearate and talc, and were compressed on a 10-station rotary tablet compression machine (Rimek Minipress-I) fitted with 4 mm round, plain punches, with compression force adjusted to achieve a target hardness of approximately 5 kg/cm². For tablet preparation, the PEC was weighed out in a quantity equivalent to the combined initial SLBG and CGG loading specified for the corresponding formulation, rather than the net weight of the recovered complex itself.

The compressed tablets were evaluated for post-compression characteristics like appearance, thickness, hardness, weight variation and drug content. *In vitro* dissolution of RLPC tablets was carried out in 0.1 N HCl for 2 h, followed by pH 6.8 phosphate buffer for a further 10 h, in accordance with the standard two-stage compendial protocol used to simulate sequential gastric and intestinal transit for controlled release dosage forms. Dissolution of pure losartan potassium powder, at the rabbit equivalent dose, was carried out under identical two-stage conditions for comparison.

2.5. Ethical approval

All animal procedures were reviewed and approved by the Institutional Animal Ethics Committee (IAEC) of Flair

Labs,surat,Gujarat, with approval number 1250/PO/RcBi/S/09/CPCSEA and protocol number 1250/PO/RcBi/S/24/CPCSEA, dated 21 august 2024, and were conducted in accordance with the institution's standard guidelines for the care and use of laboratory animals.

2.6. Study design

A single-dose, parallel-group pharmacokinetic study was performed in healthy rabbits randomly allocated to two groups of six animals each. Group I (reference) received 1 mL of a losartan potassium dispersion (6.5 mg) prepared in 1% w/v sodium carboxymethyl cellulose. Group II (test) received the rabbit dose optimised RLPC tablet, containing an equivalent dose of losartan potassium.

2.7. Study procedure

Animals were fasted overnight before dosing, with free access to water maintained throughout the fasting period. Dosing was performed by the oral gastric gavage technique: each rabbit was gently restrained and a mouth gag was placed to keep the oral cavity open, and a lubricated, sterile feeding tube (14 Fr nasogastric tube, 4.7 mm outer diameter) was passed carefully into the stomach, avoiding tracheal placement. Correct positioning was confirmed by passing 0.5 mL of water through the tube and verifying unobstructed flow. Group I animals received the losartan potassium dispersion via the feeding tube, followed by 2 mL of distilled water; Group II animals received the RLPC tablet placed into the feeding tube and flushed into the stomach with 2 mL of water. Water was available ad libitum throughout the study, and food was reintroduced 2 h after dosing.

2.8. Blood sample collection

Blood samples (0.3-0.5 mL) were withdrawn from the marginal ear vein using a sterile 24-gauge needle inserted against the direction of blood flow, before dosing (0 h) and at 0.5, 1, 2, 4, 6, 8, 10, 12, 18 and 24 h post dose, and were collected into EDTA coated microcentrifuge tubes. The cumulative volume of blood withdrawn over the course of the study did not exceed 1% of each animal's body weight, in accordance with institutional animal ethical guidelines for blood collection[5]. Samples were centrifuged at 2000 rpm for 10 min, and the separated plasma was stored at -20°C until analysis.

2.9. Plasma sample analysis

Plasma losartan potassium concentrations were determined using a previously validated HPLC-PDA bioanalytical method. Briefly, 200 µL of plasma was mixed with 100 µL of valsartan internal standard solution (2000 ng) and 500 µL of acetonitrile, and the mixture was diluted with mobile phase to a final volume of 2 mL, vortexed for 2 min, and centrifuged at 10,000 rpm for 10 min. A 10 µL aliquot of the supernatant was injected onto a Waters Alliance HPLC system equipped with a quaternary pump and photodiode array detector, using an Inertsil ODS column at a mobile phase flow rate of 1 mL/min.

2.10. Pharmacokinetic parameters

Pharmacokinetic parameters were derived from the mean plasma concentration-time data by a standard non-compartmental approach using Microsoft Excel[6–8]. The area under the plasma concentration–time curve from zero to the last quantifiable time point (AUC_{0-t}) was calculated by the linear trapezoidal rule (Eq. 1)[6], and the area under the curve extrapolated to infinity ($AUC_{0-\infty}$) was obtained as the sum of AUC_{0-t} and the residual area (C_t/k_{el}) (Eq. 2).

$$AUC_{0-t} = \int_0^t C(t)\,dt \quad \text{(Eq. 1)}$$

$$AUC_{0-\infty} = AUC_{0-t} + C_t/k_{el} \quad \text{(Eq. 2)}$$

where Ct is the last measured plasma concentration and kel is the terminal elimination rate constant, calculated from the slope of the terminal log-linear segment of the plasma concentration-time curve (k_{el} = -slope × 2.303).

The absorption rate constant (k_a) was determined by the Wagner-Nelson method[9,10], based on the differential equation relating the amount absorbed to the apparent volume of distribution (V_d) and plasma concentration. Integration and normalization with respect to volume of distribution yielded the fraction absorbed at each sampling point (Eq. 4):

$$A_t/V_d = C_t + k_{el}(AUC_{0-t}) \quad \text{(Eq. 3)}$$

where A_t is the cumulative amount of drug absorbed at time t. The asymptotic maximum value, $(A_t/V_d)_\infty$, was determined from the data, and the percentage fraction absorbed at each time point was calculated as $[(A_t/V_d)/(A_t/V_d)_\infty] \times 100$. A semi-logarithmic plot of percentage drug unabsorbed against time was used to characterize the absorption phase, and k_a was obtained from the slope of this plot (k_a = slope × 2.303).

The apparent elimination half life ($t_{1/2}$), Mean residence time (MRT), Apparent total body clearance (Cl/F) and apparent volume of distribution (Vd/F) were calculated from Eq. 5-8 respectively[7,8].

$$t_{1/2} = 0.693 / k_{el} \quad \text{(Eq. 5)}$$

$$MRT_{0-\infty} = AUMC_{0-\infty} / AUC_{0-\infty} \quad \text{(Eq. 6)}$$

$$Cl/F = Dose / AUC_{0-\infty} \quad \text{(Eq. 7)}$$

$$V_d/F = Dose / (k_{el} \times AUC_{0-\infty}) = (Cl/F) / k_{el} \quad \text{(Eq. 8)}$$

2.11. Statistical analysis

Pharmacokinetic parameters obtained from the pure drug (reference) and RLPC (test) groups were compared using an unpaired Student's t-test[11], performed in Microsoft Excel, with a probability level of $p < 0.05$ taken as statistically significant.

2.12. *In vitro–in vivo* correlation (IVIVC)

An exploratory Level A IVIVC was constructed for the RLPC formulation, in line with FDA guidance on the development and evaluation of *in vitro-in vivo* correlations for extended-release oral dosage forms[12], by comparing the in vitro fraction of drug dissolved with the *in vivo* fraction absorbed at the corresponding common sampling points (up to 12 h). The *in vivo* fraction absorbed, Fa(t), was estimated for each rabbit from the individual plasma concentration-time data using a deconvolution based approach (Eq. 9 and Eq. 10), and the mean percentage fraction absorbed ($\%F_a$) at each time point was plotted against the corresponding percentage fraction dissolved in vitro.

$$F_a(t) = [C_t + k_{el}(AUC_{0-t})] / [k_{el}(AUC_{0-\infty})] \quad \text{(Eq. 9)}$$

$$\%F_a = F_a \times 100 \quad \text{(Eq. 10)}$$

RESULTS AND DISCUSSION

3.1. Rabbit dose calculation and characteristics of the

RLPC tablet

Based on the body surface-area conversion method, the calculated dose of losartan potassium for a rabbit weighing approximately 2.5 kg was 6.5 mg. The optimized LPC formula was downsized proportionately on this basis to obtain the RLPC composition, retaining the same relative ratio of SLBG, CGG and MCC as the optimized LPC tablet (Table 1), and was prepared under identical processing conditions.

The RLPC tablets met the target hardness of approximately 5 kg/cm² and were evaluated for post-compression characteristics, which are summarized in Table 2. Appearance, thickness, hardness, weight variation and drug content of RLPC tablets all complied with acceptable Pharmacopeial limits and were comparable to those of the LPC tablets, confirming that the downscaling process did not compromise tablet quality. A friability test was not performed on the RLPC batch because the large number of tablets required for this assay was not justified, given that the RLPC batch was prepared solely to support the in vivo pharmacokinetic study.

3.2. *In vitro* dissolution profile of RLPC and comparison with LPC

The *in vitro* dissolution profiles of pure losartan potassium powder and the RLPC tablets, compared against the previously obtained dissolution data for the optimized LPC formulation, are illustrated in Figure 1. Dissolution of the pure drug was essentially complete within 1 hour, consistent with the high aqueous solubility and rapid intrinsic dissolution of the potassium salt. In contrast, the RLPC and LPC tablets exhibited closely overlapping release profiles over the full 12 hour period, each showing a similar, gradually increasing release pattern with no significant divergence at any sampling interval. This overlap indicates that the proportionate downscaling of the PEC based formulation preserved the polymer to drug ratio responsible for the controlled release behaviour and confirms that the RLPC tablet was suitable for use as the test formulation in the subsequent in vivo pharmacokinetic evaluation.

3.3. *In vivo* pharmacokinetic study

Losartan potassium has a reported elimination half life of approximately 2 h[13], and blood sampling was therefore extended to 24 h to capture the complete plasma concentration-time profile, including the terminal elimination phase, in both treatment groups. The mean plasma concentrations obtained following administration of the pure drug and the RLPC tablet are presented in Table 3 and Table 4, respectively, with the corresponding concentration-time profiles illustrated in Figure 2 and Figure 3; the comparative mean plasma concentration-time profiles of both treatments are shown together in Figure 4.

3.4. Pharmacokinetic parameters

The pharmacokinetic parameters derived from the mean plasma concentration data of both treatment groups C_{max}, T_{max}, k_a, k_{el}, $t_{1/2}$, AUC_{0-t}, $AUC_{0-\infty}$, $AUMC_{0-\infty}$ and MRT are summarized in Table 5.

The mean peak plasma concentration (C_{max}) was 356.42 ng/mL for pure losartan potassium and 304.33 ng/mL for the RLPC tablet. The lower C_{max} observed for RLPC coincided with a marked delay in the time to reach peak concentration (T_{max}), which increased from 1 h for the pure drug to 6 h for the RLPC tablet. The delayed T_{max} together with the reduced C_{max} reflects a slower, more gradual release of drug from the RLPC tablet, consistent with sustained absorption and prolonged systemic availability rather than a rapid, bolus-like input.

This delayed T_{max} is consistent with the pharmacokinetic behaviour reported for other controlled- and sustained-release losartan potassium formulations. An effervescent floating matrix tablet of losartan potassium in albino rabbits reported a T_{max} of 4.1 h, compared with 1.5 h for an oral drug solution, with mean residence time increasing from 4.22 h to 18.92 h[2]. Similarly, sustained-release losartan potassium pellets exhibited a T_{max} of 9.72 ± 2.22 h compared with 2.11 ± 0.49 h for an immediate-release tablet, confirming prolonged drug absorption from the modified-release formulation[14]. The 6 h T_{max} observed for RLPC in the present study is therefore consistent with previously reported controlled-release losartan formulations[2,14] and supports the intended prolonged-release characteristics of the developed PEC-based tablet[15].

The extent of drug absorption, reflected in the AUC, provided further evidence of the enhanced systemic exposure achieved with RLPC. AUC_{0-t} increased from 1065.78 ng·h/mL for pure losartan potassium to 3596.44 ng·h/mL for RLPC (approximately 3.4-fold), while $AUC_{0-\infty}$ increased from 1113.81 ng·h/mL to 4201.65 ng·h/mL (approximately 3.8-fold), indicating a substantial enhancement in the extent of drug exposure following administration of the RLPC tablet; this increase is attributable to the controlled, sustained release of drug from the PEC matrix rather than to any change in the intrinsic disposition of the drug.

AUMC provided complementary evidence of the prolonged in vivo performance of RLPC. $AUMC_{0-t}$ increased from 3186.05 $ng \cdot mL^{-1} \cdot h^2$ for the pure drug to 21787.33 $ng \cdot mL^{-1} \cdot h^2$ for RLPC, with a proportionate increase also observed for $AUMC_{0-\infty}$ (3807.81 to 40018.82 $ng \cdot mL^{-1} \cdot h^2$), indicating that losartan potassium molecules remained in the systemic circulation for a considerably longer duration following administration as the RLPC tablet.

In controlled-release formulations where the rate of absorption is markedly slower than the rate of elimination, drug absorption becomes the rate-limiting step governing plasma drug levels, a phenomenon commonly described as flip-flop kinetics. Under such conditions, the terminal segment of the log plasma concentration–time curve reflects the absorption process rather than true elimination, and the terminal slope must instead be resolved by the method of residuals (feathering technique) to obtain an accurate estimate of k_{el}. This approach was applied for the RLPC data, allowing the absorption and elimination phases to be characterized separately and with greater accuracy.

The elimination rate constant (k_{el}) was 0.339 h^{-1} for pure losartan potassium and 0.310 h^{-1} for RLPC, corresponding to elimination half life of 2.04 h and 2.23 h, respectively. The closely comparable k_{el} and $t_{1/2}$ values between the two treatments indicate that formulating losartan potassium as a PEC-based controlled-release tablet did not alter the intrinsic elimination characteristics of the drug, consistent with the general pharmacokinetic principle that elimination is governed primarily by physiological clearance mechanisms and is largely independent of the dosage form administered.

The absorption rate constant (ka) for RLPC was 0.098 h^{-1}, considerably lower than the corresponding elimination rate constant, confirming absorption-limited (flip-flop) kinetics and demonstrating the effective drug-retardation capacity of the sulphated locust bean gum–cationic guar gum polyelectrolyte matrix. The apparent clearance (Cl/F) was 20.20 L/h for pure losartan potassium and 11.21 L/h for RLPC, with corresponding apparent volumes of distribution of 59.53 L and 36.08 L, respectively.

Mean residence time (MRT) increased nearly three-fold, from 3.41 h for pure losartan potassium to 9.52 h for RLPC, reflecting the ability of the developed PEC-based controlled-release tablet to sustain drug release and maintain plasma drug levels over a considerably longer period than the pure drug.

3.5. Statistical analysis

An unpaired Student's t-test was used to compare the pharmacokinetic parameters obtained after administration of pure losartan potassium and the optimized RLPC tablet; the results are summarized in Table 6. Statistically significant differences ($p < 0.05$) were observed for the parameters governing the extent and duration of drug exposure, namely C_{max}, k_a, AUC_{0-t}, $AUC_{0-\infty}$, $AUMC_{0-t}$, $AUMC_{0-\infty}$ and MRT, confirming enhanced systemic exposure and prolonged residence of losartan potassium with the RLPC controlled release tablet. In contrast, kel and $t_{1/2}$ did not differ significantly between the two treatments ($p > 0.05$), indicating that the observed pharmacokinetic differences arose predominantly from altered absorption and release characteristics rather than from any change in drug elimination or disposition.

Because the log transformed AUC_{0-t} and $AUC_{0-\infty}$ ratios for RLPC relative to the pure drug (approximately 3.4-fold and 3.8-fold, respectively) fell well outside the conventional 80–125% bioequivalence acceptance limits[16], the RLPC formulation could not be considered bioequivalent to pure losartan potassium in terms of systemic exposure. This outcome is expected and, indeed, desirable in the present context, since the RLPC tablet was designed specifically to modify rather than replicate the pharmacokinetic profile of the immediate release drug, and the substantially higher AUC and prolonged MRT instead confirm successful attainment of the intended controlled release pharmacokinetic behaviour.

3.6. *In vitro–in vivo* correlation (IVIVC)

The IVIVC analysis was restricted to the common sampling points shared by the *in vitro* and *in vivo* data, up to 12 h, and a Level A (point-to-point) correlation was constructed. The percentage fraction of drug absorbed following RLPC administration was calculated for each rabbit, and the mean ± SD values at each time point are presented in Table 6. The corresponding *in vitro* percentage dissolved and *in vivo* mean percentage fraction absorbed are compared in Table 8, and the resulting correlation plot is shown in Figure 5.

A strong linear relationship was observed between the in vitro dissolution and the estimated *in vivo* absorption profile of RLPC, described by the regression equation $y = 0.8845x - 1.7137$, with a coefficient of determination (R^2) of 0.9919. This close point-to-point relationship indicates that the *in vitro* dissolution profile of the optimized RLPC formulation provided a good representation of its *in vivo* absorption behaviour, supporting the use of the *in vitro* dissolution test as a reliable predictor of the formulation's *in vivo* performance.

Taken together, the *in vivo* pharmacokinetic findings demonstrate that the polyelectrolyte complex formed between sulphated locust bean gum and cationic guar gum successfully regulated the release of losartan potassium under physiological conditions, producing a controlled release absorption profile and markedly enhanced systemic exposure relative to the pure drug. This establishes the SLBG-CGG polyelectrolyte complex as an effective release-retarding matrix for the design of oral controlled-release drug delivery systems.

CONCLUSION

The *in vivo* pharmacokinetic study demonstrated that the optimized RLPC tablet successfully modified the absorption profile of losartan potassium relative to the pure drug, producing a lower peak plasma concentration with a markedly delayed T_{max}, consistent with a slower and more controlled release of drug into the systemic circulation. Significant increases in AUC, AUMC and mean residence time confirmed enhanced systemic exposure and prolonged drug availability, while the unaltered elimination rate constant and half life indicated that the polyelectrolyte matrix modified drug release without affecting the intrinsic elimination of the drug. The reduced absorption rate constant, together with absorption limited (flip-flop) kinetics, further confirmed effective control over the drug release process. A strong Level A IVIVC ($R^2 = 0.9919$) between the *in vitro* dissolution and *in vivo* absorption profiles indicated that the *in vitro* dissolution test is a reliable predictor of the *in vivo* performance of this formulation. Collectively, these findings establish the polyelectrolyte complex matrix composed of sulphated locust bean gum and cationic guar gum as an effective release retardant for the development of controlled release oral dosage forms of losartan potassium.

DECLARATIONS

Conflict of interest: The authors declare that they have no conflict of interest.

Ethical approval: This study was approved by the Institutional Animal Ethics Committee (IAEC) of Flair Labs,surat,Gujarat, approval number 1250/PO/RcBi/S/09/CPCSEA, protocol number 1250/PO/RcBi/S/24/CPCSEA, dated 21 august 2024.

Acknowledgements: None to acknowledge

TABLE AND FIGURE LEGENDS

Table 1. Composition of losartan potassium LPC and rabbit dose RLPC tablets.

Table 2. Post compression characteristics of LPC and RLPC tablets.

Table 3. Mean plasma losartan potassium concentration-time data following administration of pure drug (n = 6).

Table 4. Mean plasma losartan potassium concentration-time data following administration of RLPC (n = 6).

Table 5. Pharmacokinetic parameters of pure losartan potassium and RLPC (mean ± SD).

Table 6. Statistical comparison of pharmacokinetic parameters of pure losartan potassium and RLPC (unpaired t-test, $p < 0.05$).

Table 7. Percentage fraction of drug absorbed from RLPC in individual rabbits.

Table 8. *In vitro* percentage drug dissolved and *in vivo* mean percentage fraction absorbed for RLPC.

Figure 1. *In vitro* dissolution profiles of losartan potassium from LPC, RLPC and pure drug.

Figure 2. Plasma concentration-time profile of pure losartan potassium in rabbits (individual and mean).

Figure 3. Plasma concentration-time profile of losartan potassium following RLPC administration in rabbits (individual and mean).

Figure 4. Comparative mean plasma concentration-time profiles of pure losartan potassium and RLPC.

Figure 5. Level A *in vitro-in vivo* correlation plot for the RLPC tablet (percentage drug dissolved vs percentage fraction absorbed).

Table 1

Ingredients (mg/tablet)	LPC	RLPC
Losartan potassium	50	6.5
Sulphated locust bean gum (SLBG)	69	9
Cationic guar gum (CGG)	47	6.1
Microcrystalline cellulose (MCC)	44	5.8
Magnesium stearate	2.5	0.3
Talc	2.5	0.3
Final weight (mg)	215	28.0

Table 2

	LPC	RLPC
Thickness[a] (mm)	2.55±0.06	2.31±0.02
Hardness[a] (kg/cm^2)	5.6±0.1	5.1±0.3
Uniformity of weight[b] (mg)	215±1.2	27±0.05
Drug content[c] (%)	99.79±0.43	99.95±0.21

a: mean±s.d., n=5; b: mean±% deviation, n=20; c: mean±s.d., n=3

Table 3

Time (hours)	Plasma concentration (ng/mL) (Mean±s.d.)
0.5	129.68±4.51
1	356.42±5.60
2.0	218.32±5.89
4	104.13±5.27
6	56.512±3.80
8	28.27±4.48
10	16.30±2.86
12	n.d.

*n.d. indicates non detectable plasma drug levels

Table 4

Time (hours)	Plasma concentration (ng/mL) (Mean±s.d.)
0.5	53.92±4.01
1	126.54±6.28
2	187.35±8.32
4	231.54±10.16
6	304.33±11.18
8	289.16±4.47
10	239.36±8.12
12	178.03±5.81
16	102.78±5.17
20	59.78±4.80
24	n.d.

*n.d. indicates non detectable plasma drug levels

Table 5

Pharmacokinetic parameters	Units	Pure losartan potassium	RLPC
C_{max}	ng/mL	356.42	304.33
T_{max}	H	1	6
k_{el}	h^{-1}	0.339	0.310
k_a	h^{-1}	-	0.098
$t_{½}$	H	2.04	2.23
AUC_{0-t}	ng $mL^{-1}h^{-1}$	1065.78	3596.44
$AUC_{0-\infty}$	ng $mL^{-1}h^{-1}$	1113.81	4201.65
$AUMC_{0-t}$	ng $mL^{-1}h^{-2}$	3186.05	21787.33
$AUMC_{0-\infty}$	ng $mL^{-1}h^{-2}$	3807.81	40018.82
MRT	H	3.41	9.52
Cl/F	L h^{-1}	20.20	11.21
V_d/F	L	59.53	36.08

Table 6

Parameters	Units	Inference
C_{max}	ng/mL	Significant
k_a	h^{-1}	Significant
AUC_{0-t}	ng $mL^{-1}h^{-1}$	Significant
MRT	H	Significant
$t_{½}$	H	Non-Significant
k_e	h^{-1}	Non-Significant

Table 7

Time (hours)	Percentage fraction absorbed from RLPC (%) (Mean±s.d.)
0.5	4.57 ± 0.24
1	11.44 ± 0.29
2	20.35 ± 0.36
4	34.92 ± 0.95
6	54.81 ± 0.78
8	69.38 ± 0.90

10	79.49 ± 0.62
12	85.76 ± 0.66

Table 8

Time (hours)	% drug dissolved	Mean %fraction drug absorbed
0.5	5.21	4.57
1	15.06	11.44
2	23.01	20.35
4	48.19	34.92
6	65.14	54.81
8	78.63	69.38
10	88.11	79.49
12	99.98	85.76

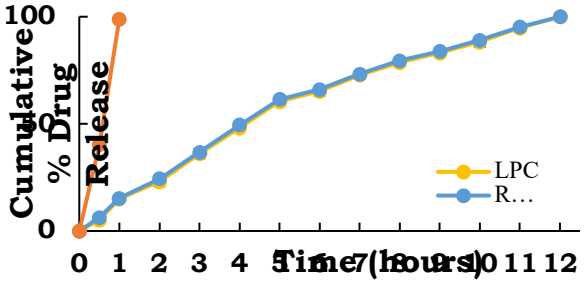

Figure 1

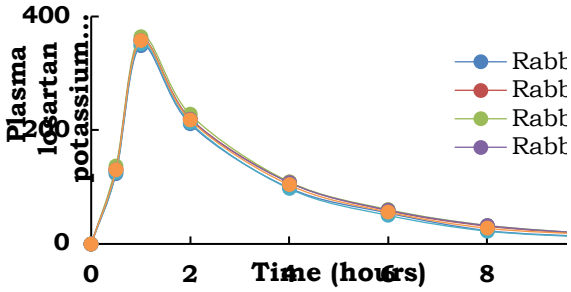

Figure 2

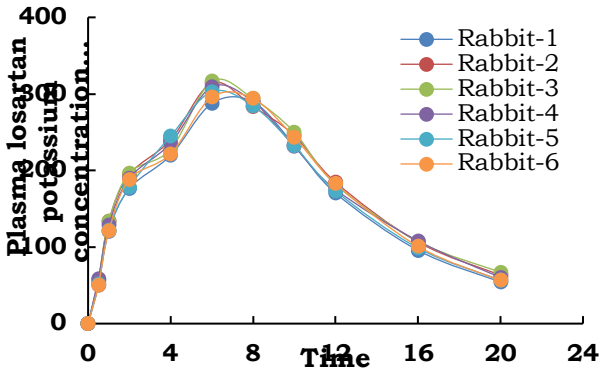

Figure 3

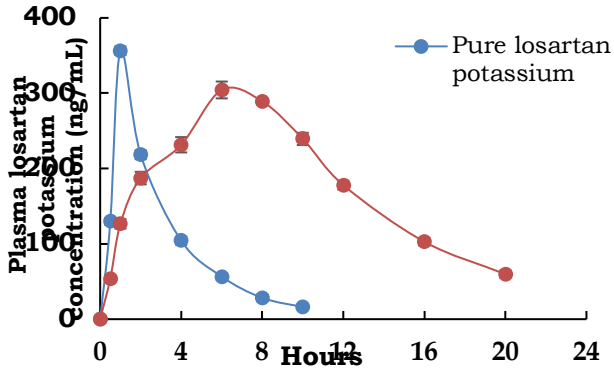

Figure 4

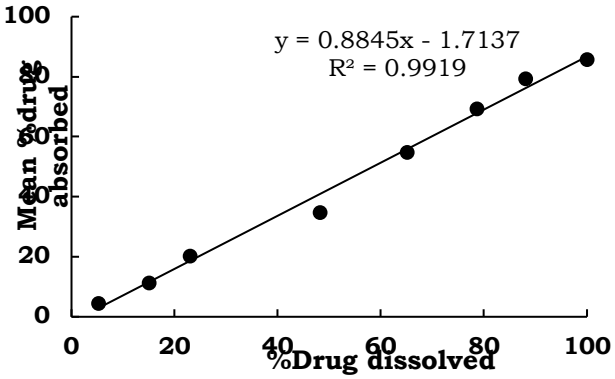

Figure 5

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